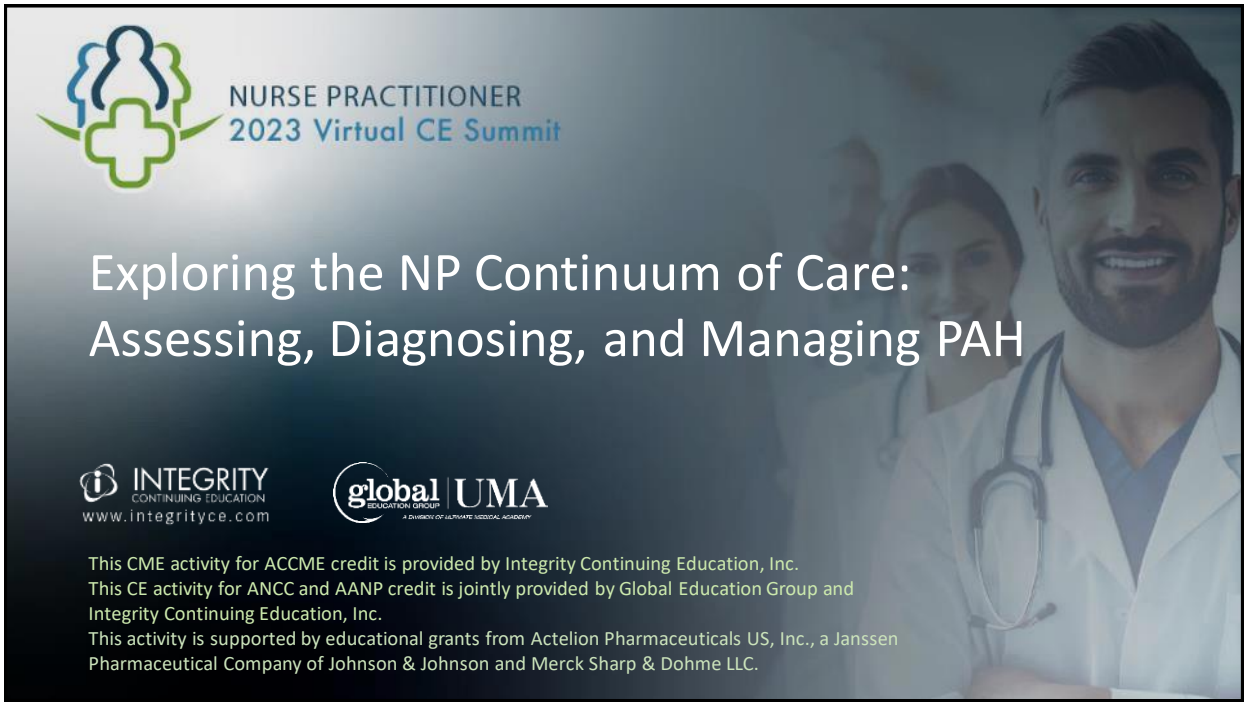

Learning Objectives

- Delineate signs, symptoms, and risk factors that should raise the index of suspicion for pulmonary arterial hypertension (PAH)
- Identify patients who would benefit from referral to a cardiopulmonary specialist or PH/PAH specialty center to facilitate earlier diagnosis and treatment
- Design treatment plans that utilize current and emerging therapeutic regimens, including dual and triple combinations

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Pretest Polling Questions

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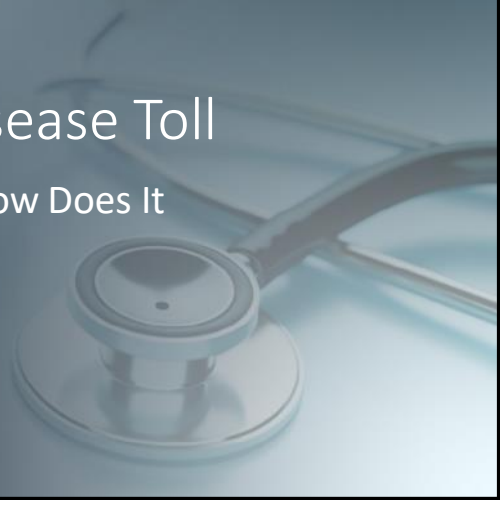
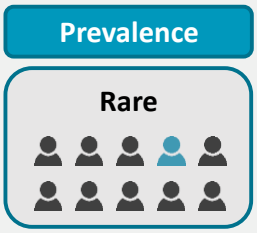
PAH Definitions and Disease Toll

What is PAH? Who Gets It? And How Does It Affect Them?



PAH Epidemiology

- Prevalence: 1% of global population
- Incidence: ~500–1,000 new cases annually in US
- Idiopathic PAH 50%–60% of all PAH cases



- **PAH 3–5 times more frequent in women**
  - Age of onset usually between 30–60
  - Frequently affects younger women
  - Can occur in all sexes and ages, even infants

PH, pulmonary hypertension.

American Lung Association. Available at: https://www.lung.org/lung-health-diseases/lung-disease-lookup/pulmonary-arterial-hypertension/learn-about-pulmonary-arterial-hypertension; Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

Hemodynamic Definition of PAH

PAH causes restricted blood flow through pulmonary arterial circulation resulting in increased PVR; this causes increased workload for the right ventricle, ultimately leading to right heart failure

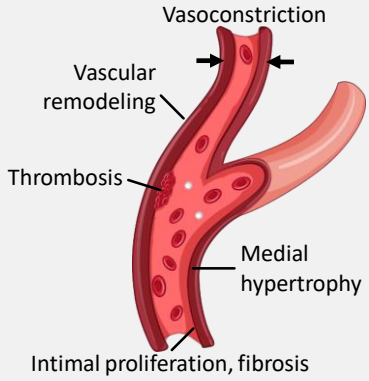
Historic Hemodynamic Definition of PAH	New Hemodynamic Definition of PAH
▪ mPAP ≥25 mmHg	▪ mPAP >20 mmHg at rest
▪ PAWP ≤15 mmHg	▪ PVR >2 Wood units
▪ PVR >3 Wood units	▪ PAWP ≤15 mmHg

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance.

Humbert M, et al. *Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879; Simonneau G, et al. *Eur Respir J.* 2019;53:1801913.

PAH Visualized: Part 1

Pulmonary Remodeling



Pulmonary artery | **Vascular obstruction**

Right Heart Failure

Right ventricular remodeling/dysfunction

Humbert M, et al. *Eur Heart J*. 2022;43:3618-3731; Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

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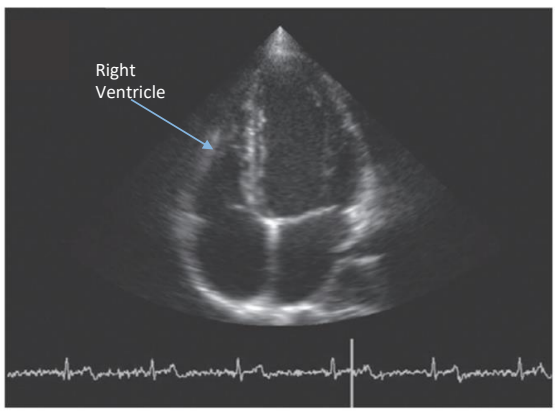
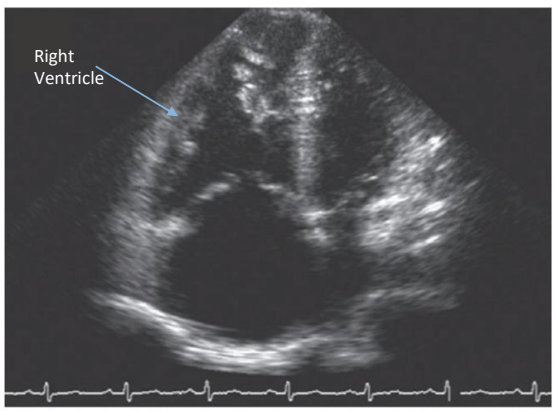
PAH Visualized: Part 2

PAH by echocardiography

Normal echo

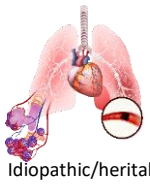
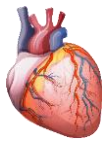
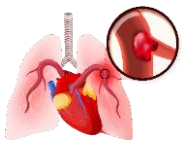


Echo in PAH



World Health Organization PH Classifications

Pulmonary hypertension (PH)

Group 1	Group 2	Group 3	Group 4	Group 5
Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Nonsevere PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Hematologic disorders • Systemic disorders

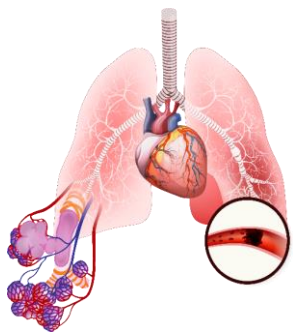
CpcPH, combined post- and pre-capillary PH; CTEPH, chronic thromboembolic PH; IpcPH, isolated postcapillary PH.

Humbert M, et al. *Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879; Simonneau G, et al. *Eur Respir J.* 2019;53:1801913.

PAH = WHO Group #1 and Subtypes

Group 1

PAH



Subtypes
1.1 Idiopathic 1.1.1 Nonresponders to vasoreactivity testing 1.1.2 Acute responders to vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with: 1.4.1 Connective tissue disease (eg, scleroderma) 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn

HIV, human immunodeficiency virus; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

Humbert M, et al. *Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

PAH Prognosis

- Mean survival of 2.8 years without treatment[1]
- With treatment, 5-year survival rates almost 70%[2,3]
  - Survival improves with early diagnosis and combination treatment

THERAPEUTIC STRATEGIES

Medical Therapy

- **PAH drugs**
- **Calcium channel blockers in responders**
- **Lung transplantation**

1. McLaughlin VV, et al. *Circulation*. 2022;106:1477-1482. 2. Doyle-Cox C, et al. *Pulm Circ*. 2019;9:2045894019855611. 3. Levine DJ. *Am J Man Care*. 2021;27:S35-S41.

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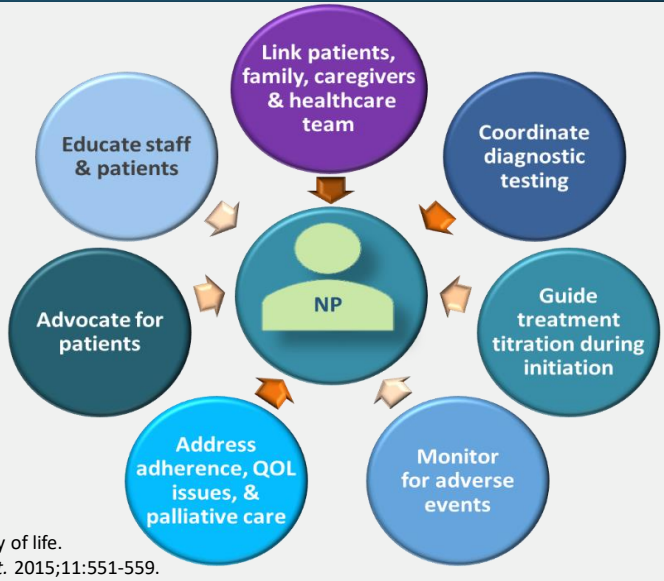
Role of NPs in PAH Diagnosis and Management



NP, nurse practitioner; QOL, quality of life.
Wapner J, Matura LA. *J Nurse Pract.* 2015;11:551-559.

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Interactive Patient Case Study

Case Study Introduction

- Rachel, African American age 32, presents with progressive dyspnea that has lasted 4 months
  - Breathlessness, light-headedness when climbing stairs
  - Unusual fatigue during the day
  - Denies chest pain, syncope, or palpitations
  - Was diagnosed with scleroderma 9 months ago

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? Discussion Polling Question #1

Other than the presence of dyspnea and breathlessness, what is the biggest clue that Rachel might have PAH?

A. Duration of the dyspnea
B. Being female/right age group
C. Experiencing unusual fatigue
D. She has scleroderma

Responses to Polling Question #1

- All clues should work together to raise the index of suspicion that Rachel may have PAH
  - Biggest indicator: **scleroderma**
    - Connective tissue disease such as scleroderma, lupus, or Sjögren's are disease drivers in ~30% of PAH cases
    - Scleroderma also more common in African American women
  - **Duration of dyspnea:** Cardinal symptom in PAH but not definitive
  - **Female/right age:** Many PAH patients are female with symptoms that start in early 30s, but not most important indicator
  - **Fatigue: C**ommon to PAH as well as many other diseases; not specific to PAH

? Discussion Polling Question #2

According to the REVEAL Registry of the United States, how long does it take, on average, for a patient to receive an accurate diagnosis of PAH?

A. 9 months
B. 18 months
C. 24 months
D. 34 months

Responses to Polling Question #2

- 34 months to diagnosis on average[1]
  - According to US-based REVEAL registry of ~3,000 patients
- Most patients present with advanced disease[2,3]
  - Diagnosis at earlier stage may make treatments more effective

1. Swinnen K, et al. *Eur Respir Rev*. 2019;28:190050. 2. Humbert M, et al. *Eur Heart J*. 2022;43:3618-3731.
3. Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

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Detecting and Diagnosing PAH

Diagnostic, assessment, and monitoring

PAH's Continuum of Clinical Manifestations

Symptoms

- Dyspnea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnea when bending forward (bendopnea)
- Palpitations
- Hemoptysis
- Exercise-induced abdominal distention and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

WHO-FC, World Health Organization-Functional Class.

Humbert M, et al. *Eur Heart J*. 2022;43:3618-3731; Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

WHO/NYHA Functional Class Assessments

WHO	NYHA	Activity Levels and Descriptions
I	1	**No limitation on physical activity.** Mostly symptom free when physically active and resting
II	2	**Slight limitation on physical activity.** No symptoms at rest, but undue shortness of breath, fatigue, chest pain or near syncope with ordinary physical activities such as climbing stairs, grocery shopping, or making the bed
III	3	**Marked limitation on physical activity.** Comfortable while resting but greatly limited by shortness of breath when performing normal household chores
IV	4	**Inability to carry out any physical activity.** Mild symptoms while at rest and severe symptoms while physically active. Symptoms of right-sided heart failure are present

NYHA, New York Heart Association.

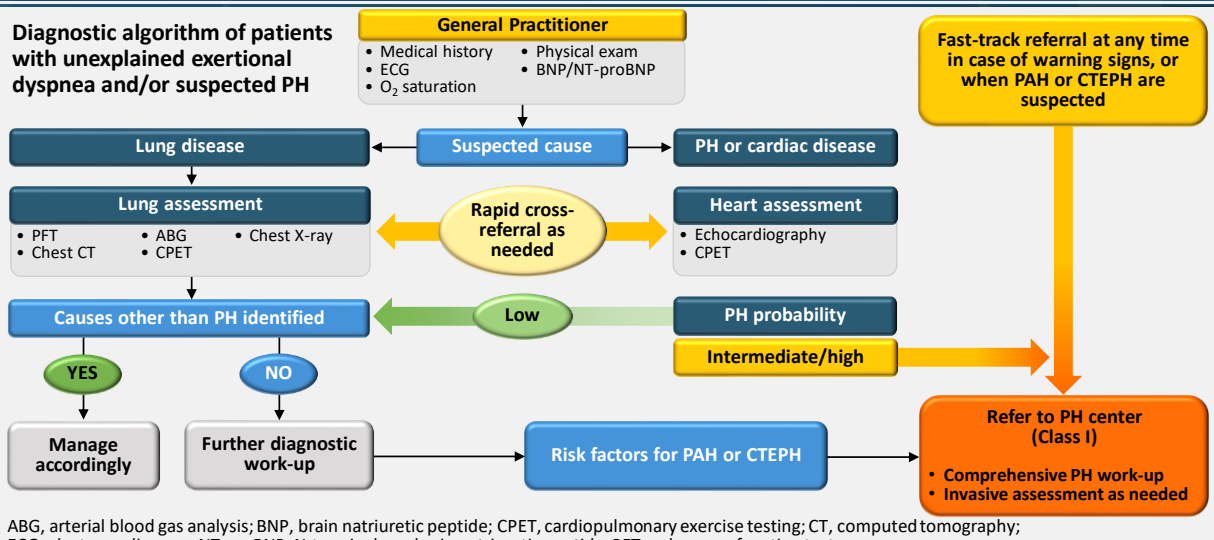
Keshavarz A, et al. *Expert Opin Drug Deliv*. 2020;17:439-461.

New Diagnostic Algorithm & PH Center Referral

- Diagnostic algorithm simplified by 2022 ESC/ERS guidelines to 3-step approach
  - Suspicion by 1st-line clinicians should lead to confirmation with RHC in PH specialty centers
  - Referral to PH specialty center when immediate or high probability of PH is established
    - Or if risk factors for PAH are present
- Simplified algorithm may facilitate earlier diagnosis

ESC/ERS, European Society of Cardiology/European Respiratory Society; RHC, right-heart catheterization.

2022 ESC/ERS Simplified Diagnostic Algorithm



ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFT, pulmonary function test.

Humbert M, et al. *Eur Heart J*. 2022;43:3618-3731; Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

Processes in PH/PAH Center

Patient care pathway and clinical management protocol
Steps from diagnosis to follow-up including advanced disease, palliative stage, and end of life

MDT meeting
Regular meetings to discuss multidisciplinary aspects of individual patient care

Patient empowerment and advocacy
Clear verbal and written information for patients that describes diagnostic procedures and treatment options; shared decision-making, collaboration with advocacy group

Interaction with external healthcare providers and other relevant stakeholders
GP, local specialist, social services, rehabilitation centers, national health services, labs, insurers, school, work, sports club, psychologist, etc

Research, training, and education
Involvement in clinical and translational research: teaching courses on local, national, or international basis

GP, general practitioner.

Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

Additional Tests to Consider

- Lab tests
  - CBC
  - CMP
  - ESR
  - CRP
  - ANA
  - ANCA
  - dsDNA (to test for lupus)
  - Toxicology screen
  - HIV
  - Hep B and C
- Imaging tests
  - HRCT
  - PFTs
  - V/Q

ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CTPA, CT pulmonary angiogram; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; V/Q, ventilation/perfusion.

Risk Assessment Tools: REVEAL

- REVEAL 2.01
  - Widely used risk calculator to predict survival
  - Uses 13 variables in:
    - Clinical tests, medical history, WHO/NYHA FC
- REVEAL Lite 2.0
  - Abridged, validated version of REVEAL 2.0
  - Can predict low-, intermediate-, high-risk 1-year survival
  - Uses 6 noninvasive variables:
    - WHO/NYHA FC
    - Systolic BP and HR
    - 6MWT
    - BNP/NT-proBNP
    - Renal insufficiency through eGFR

6MWT, 6-minute walk test; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate.

1. MD+Calc. REVEAL Registry Risk Score 2.0 for PAH calculator. Available at: https://www.mdcalc.com/calc/10071/reveal-registry-risk-score-pulmonary-arterial-hypertension-pah 2. Benza RL, et al. *Chest*. 2021;159:337-346.

ERS/ESC 3-Strata Risk Assessment Tool

Determinants 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
6-minute walking distance	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% predicted) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% predicted) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 mL/min/kg (<35% predicted) 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, cardiac magnetic resonance imaging)	Right atrium area <18 cm^2 No pericardial effusion	Right atrium area 18–26 cm^2 No or minimal, pericardial effusion	Right atrium area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mmHg Cardiac index ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg Cardiac index 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg Cardiac index <2.0 L/min/m^2 SvO_2 <60%

RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; VE/VCO_2, minute ventilation-carbon dioxide output; VO_2, oxygen uptake.

Galie N, et al. *Eur Heart J.* 2016;37:67-119.

2022 ESC/ERS Simplified 4-Strata Risk Assessment Tool

- Redefined from 3-strata tool that had one intermediate-risk category
  - For use ***follow-up assessments***
  - simplified

Determinants of Prognosis	Low Risk	Intermediate-Low Risk	Intermediate-High Risk	High Risk
Points assigned	1	2	3	4
WHO-FC	I or II	—	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

6MWD, 6-minute walking distance.

Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

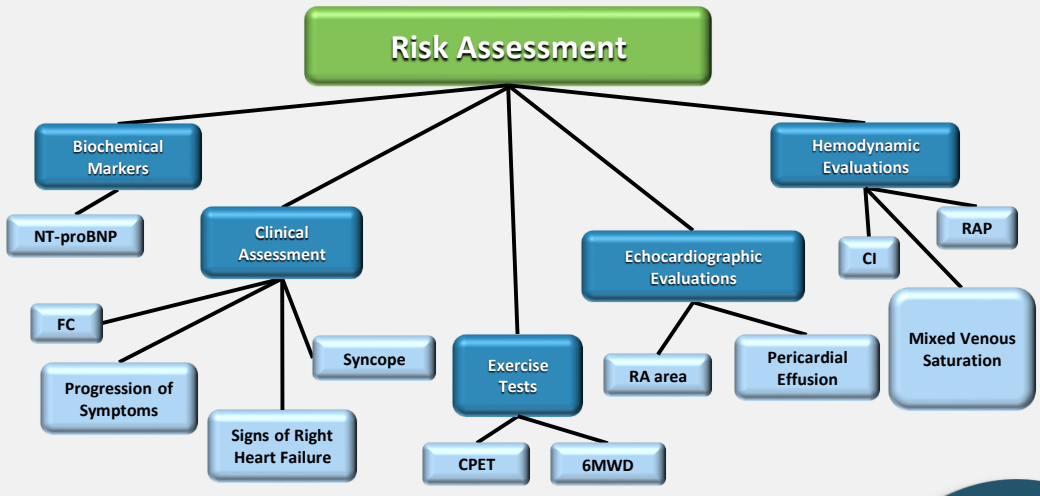
ESC/ERS: Testing Recommendations for Monitoring

Test/Assessment	At Baseline	Every 3–6 Months	Every 6–12 Months	3–6 Months After Tx Changes	At Cinical Worsening
Functional assessment	✓	✓	✓	✓	✓
ECG	✓	✓	✓	✓	✓
6MWT	✓	✓	✓	✓	✓
CPET	✓		✓		✓
Echo	✓		✓	✓	✓
Basic labs	✓	✓	✓	✓	✓
Extended labs*	✓		✓		✓
Blood gas analysis†	✓		✓	✓	✓
RHC	✓		✓	✓	✓

*Thyroid stimulating hormone, troponin, uric acid, iron status, others. †From arterial or arterialized capillary blood; peripheral oxygen saturation in stable patients or if blood gas analysis is not available. Tx, treatment.

Galiè N, et al. *Eur Heart J*. 2016;37:67-119; Humbert M, et al. *Eur Heart J*. 2022;43:3618-3731; Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

Multiparameter Risk Assessment for Continued Monitoring



CI, cardiac index; RA, right atrium.

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

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PAH Treatments

Currently available treatments and new guidelines

Goals for PAH Therapy

LT, lung transplantation.

Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

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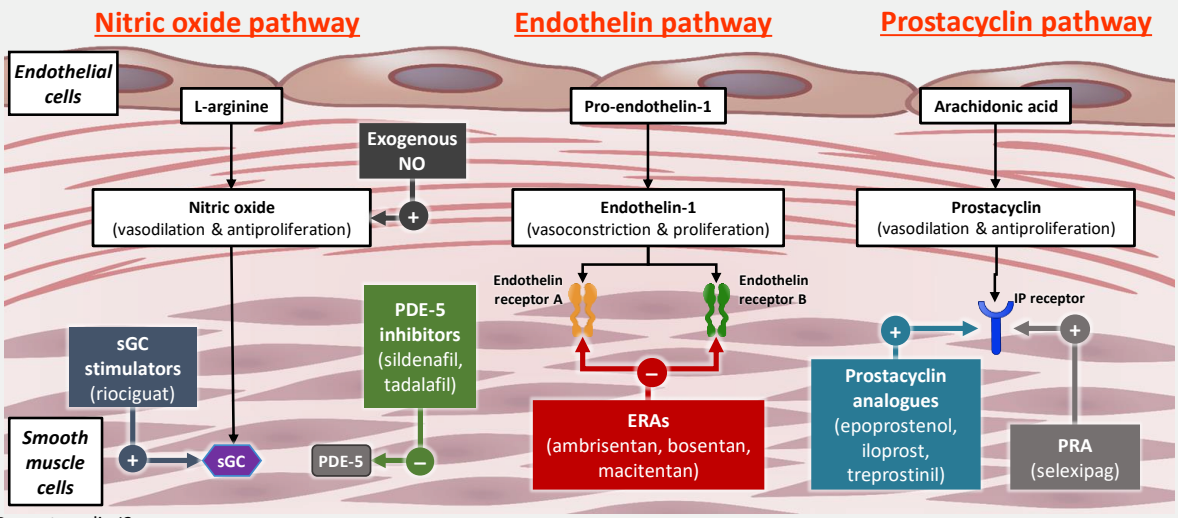
Overall PAH Treatment Goal

Achieve *low-risk status*, typically associated with:

Better exercise capacity
Improved quality of life
Good RV function
Low mortality risk

RV, right ventricle.
Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

3 Molecular Targets of Approved PAH Treatments



IP, prostacyclin I2.
Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

Medications Approved for PAH

Class	Name* (Trade Name) / Year Approved	Route	Common Class AEs	Contraindications
ERAs	Ambrisentan (Letairis) / 2007 Bosentan (Tracleer) / 2001 Macitentan (Opsumit) / 2013	Oral	Lower extremity edema, headache, anemia, hypotension, palpitations, sinusitis	Avoid in patients with liver failure. All agents available only through REMS program
sGC stimulant	Riociguat (Adempas) / 2013	Oral	Headache, dizziness, hypotension, dyspepsia, nausea, vomiting, diarrhea, constipation	No concomitant administration with nitrates and PDE-5 inhibitors. Available to women only through REMS program
PDE-5 inhibitors	Sildenafil (Revatio) / 2009 Tadalafil (Adcirca) / 2009	Oral Oral	Flushing, headache, visual disturbances, nosebleeds, hypotension, diarrhea	No concomitant administration with nitrates

*Arranged alphabetically within class. AE, adverse event; IV, intravenous; ERAs, endothelin receptor antagonists; PDE-5, phosphodiesterase-5; REMS, risk evaluation and mitigation strategies; sGC, soluble guanylate cyclase.

Leeper B, et al. *Nurs Crit Care*. 2019;14:14-22; Vasquez ZG. *Lung*. 2020;198:581-596.

Prostacyclins Approved for PAH

Class	Name* (Trade Name) / Year Approved	Route	Common Class AEs	Contraindications
PCA	Epoprostenol (Flolan) / 1995 Epoprostenol (Veletri) / 2008 Iloprost (Ventavis) / 2004 Treprostinil (Orenitram) / 2013 Treprostinil (Remodulin) / 2004 Treprostinil (Tyvaso, neb) / 2009 Treprostinil (Yutrepia, DPI) / 2021 Treprostinil (Tyvaso, DPI) / 2022	IV IV INH Oral IV & SC INH INH INH	Flushing, headache, jaw pain, diarrhea, tachycardia, hypotension; cough with inhaled preparations	Titrated for effect, titration can take place over days to weeks. Maximum dose determined by AE reactions
PRA	Selexipag (Uptravi) / 2015†	Oral	Headache, dizziness, hypotension, dyspepsia, nausea, vomiting, diarrhea, constipation	No concomitant administration with nitrates and PDE-5 inhibitors. Available to women only through REMS program

*Arranged alphabetically within class. †Intravenous formulation of selexipag approved in 2021. INH, inhaled; PCA, prostacyclin analogue; PRA, prostacyclin receptor agonist; SC, subcutaneous.

Leeper B, et al. *Nurs Crit Care.* 2019;14:14-22; Vasquez ZG. *Lung.* 2020;198:581-596.

Newest Formulation of treprostinil

- Most agents available since early or mid-2000s
- Treprostinil DPI (Tyvaso) approved in May 2022 based on open-label BREEZE trial (N=51)
  - Patients previously treated with treprostinil nebulizer
  - Significant improvements in 6MWD
  - No significant drug-related AEs

DPI, dry powder inhaler.
Spikes LA, et al. *Pulm Circ*. 2022;12:e12063.

Benefits and Drawbacks of Inhaled Therapies

Advantages

- Local delivery, higher drug concentration to lungs, enhancing efficacy
- Mitigation of systemic AEs, including hypotension
- Vasodilation improves V/Q and gas exchange
- Rapid drug absorption and faster onset of action

Disadvantages

- Irritant effects on airways
- Limitation of medication dose due to airway symptoms
- Delivery systems can be cumbersome and time consuming
- Can be very costly

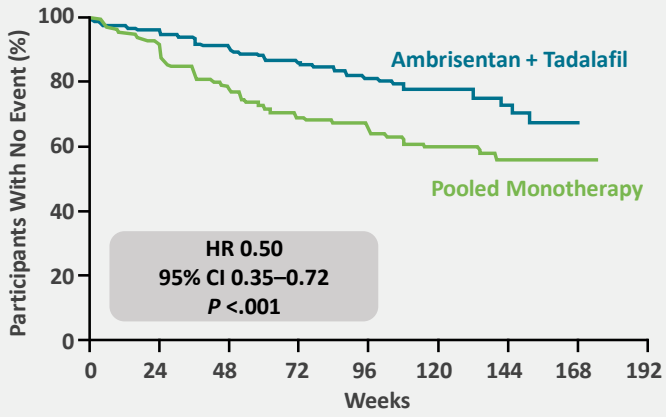
Keshavarz A, et al. *Expert Opin Drug Deliv*. 2020;17:439-461.

Guideline Changes Based on Dual Therapy Trials

- Combination therapies maximize synergies between the 3 pathways, molecular targets, and drug classes
- ESC/ERS 2022 recommendation: Newly diagnosed patients with low- or intermediate-risk should be rstarted on an ERA + PDE-5 inhibito

Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

AMBITION: Dual Therapy in Newly Diagnosed PAH



Combination: AMB (ERA) + TAD (PDE-5 inhibitor)

Treatment Arms: AMB + TAD (COMBO, n=253) vs AMB ***or*** TAD (MONO, n=247)

Primary endpoint: Time to clinical failure

Findings:

- Clinical failure ↓ with COMBO vs MONO (*P* <.001)
- COMBO therapy showed greater ↓ from baseline in NT-proBNP and clinical response rate but ↑ in 6MWT
- AEs more common with COMBO vs MONO: peripheral edema, headache, nasal congestion, anemia

AMB, ambrisentan; CI, confidence interval; COMBO, combination therapy; HR, hazard ratio; MONO, monotherapy; TAD, tadalafil.

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

TRITON: Triple vs Dual Therapy for Newly Diagnosed PAH

Newly diagnosed, treatment-naïve patients with PAH

n=123	Macitentan 10 mg OD	Tadalafil 40 mg OD	Selexipag 200-1600 µg BID
n=124	Macitentan 10 mg OD	Tadalafil 40 mg OD	Placebo 200-1600 µg BID

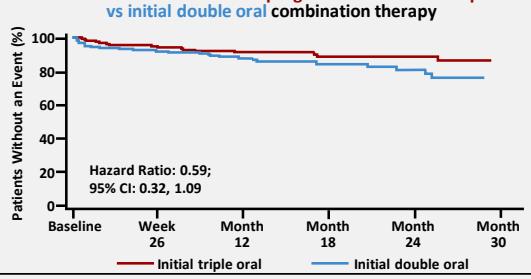
Change from Baseline to Week 26

	Initial triple	Initial double	Treatment effect
Primary Endpoint			
Pulmonary vascular resistance	-54%	-52%	No difference
Secondary Endpoints (Exploratory Analyses)			
6-minute walk distance	+55 m	+56 m	No difference
NT-proBNP	-74%	-75%	

Time to First Disease Progression Event

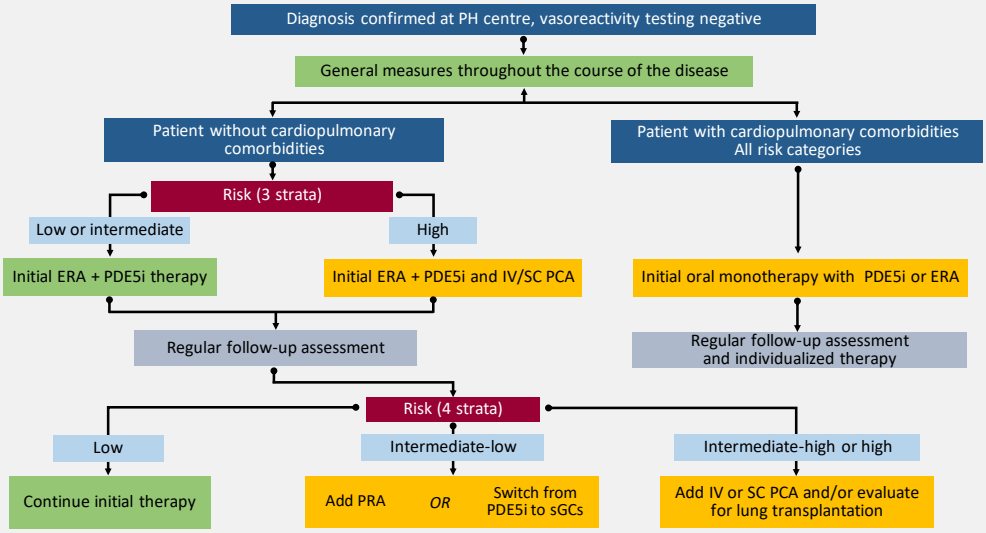
Secondary Endpoints (Exploratory Analyses)

41% reduction in risk of disease progression with initial triple oral vs initial double oral combination therapy



Chin KM, et al. *J Am Coll Cardiol.* 2021;78:1393-1403.

2022 ESC/ERS Treatment Algorithm



Humbert M, et al. *Eur Heart J.* 2022;43:3618-3731; Humbert M, et al. *Eur Respir J.* 2023;61:2200879.

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Emerging PAH Treatments

Medications in Late-Phase Trials

Emerging Treatments in Ongoing Trials

Drug Name*	Mechanism	Route	Trial Name (ID Number)	Trial Phase	Number Enrolled	Study Completion
MK-5474	sGC stimulant	INH	INSIGNIA-PAH (NCT04732221)	2/3	450	Jan 2028
M/T STCT[†] (MACI + TAD)	ERA + PDE-5 inhibitor	Oral	A DUE (NCT03904693)	3	187	Sep 2024
Ralinepag	PRA	Oral	ADVANCE OUTCOMES (NCT03626688)	3	1,000	Dec 2023
Seralutinib	PDGFR antagonist	INH	OLE (NCT04816604)	2	100	Jul 2025
Sotatercept	TGF-β inhibitor	SC	ZENITH (NCT04896008)	3	166	Dec 2026
			SOTERIA (NCT04796337)	3	700	Nov 2027
			HYPERION (NCT04811092)	2	662	Aug 2028
			MOONBEAM[‡] (NCT05587712)	2	48	Sep 2028

*Arranged alphabetically. [†]Fixed-dose combination of macitentan and tadalafil; [‡]MOONBEAM is studying sotatercept in children ages 1–17 years old. MACI, macitentan; M/T, macitentan + tadalafil; PDGFR, platelet-derived growth factor; OLE, open-label extension; STCT, single tablet combination therapy; TGF-β, transforming growth factor beta.
Source: ClinicalTrials.gov, using filters for recruiting, or ongoing phase 2 or 3 trials in PAH.

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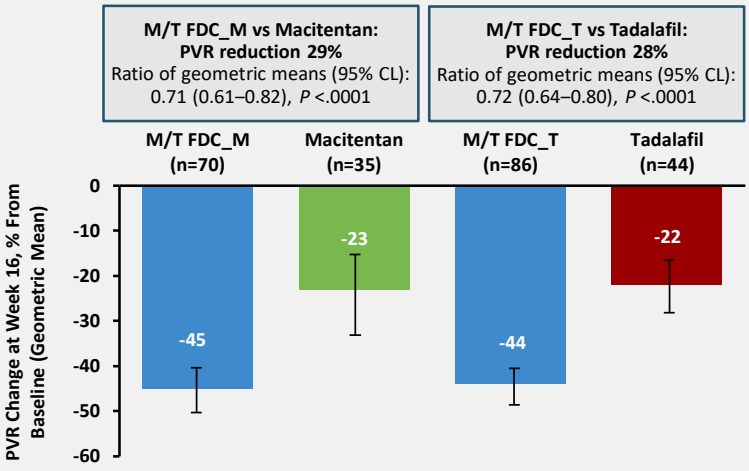
A DUE: Phase 3 Trial of Fixed-Dose Combination

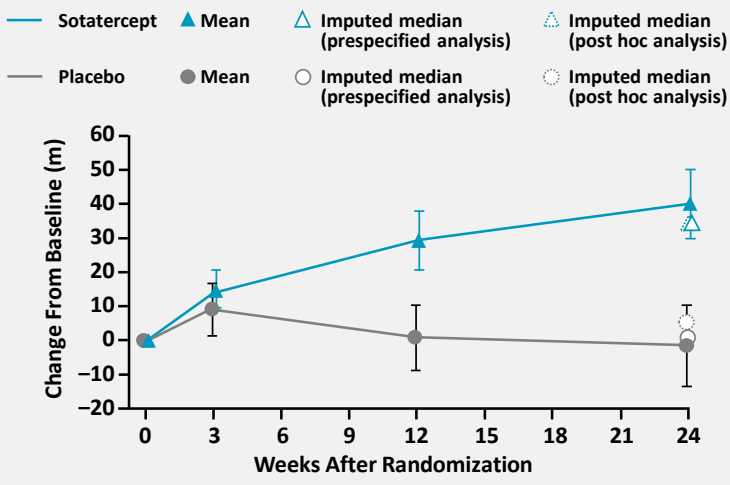


Phase 3 A DUE trial (N=187)

- M/T FDC combines macitentan 10 mg/day + tadalafil 40 mg/day
- Significant improvement in PVR with combination vs monotherapy after 15 weeks
- FDC tablet could improve adherence and simplify treatment

FDC_M, fixed-dose macitentan + tadalafil (n=70; prior-ERA users n=21, treatment-naïve n=49); M/T FDC_T, fixed-dose macitentan + tadalafil (n=86; treatment-naïve n=49, prior-PDE5i n=36).
Chin K, et al. ACC 2023, Session 409-15.

STELLAR: Phase 3 Trial Sotatercept as Add-On Treatment



Phase 3 STELLAR trial (N=323)

- **Population:** PAH WHO FC II or III randomized to sotatercept or placebo + stable background therapy
  - Dosing 0.3 mg/kg → 0.7 mg/kg Q3W
- **Primary endpoint:** Change from baseline in 6MWD
- **Efficacy:** 54 m increase in sotatercept cohort vs 1 m in placebo
- **Safety:** epistaxis, dizziness, telangiectasia; ↑ hemoglobin, thrombocytopenia, and blood pressure

Q3W, every 3 weeks.
Hoeper MM, et al. *N Engl J Med.* 2023;388:1478-1490.

SOTERIA: Phase 3 Open-Label Sotatercept

- Long-term follow-up trial (NCT04796337) with patients from phase 2 sotatercept studies (N=409)
  - **Primary endpoint:** Long-term safety and efficacy of sotatercept 0.3 or 0.7 mg/kg Q3W as add-on to background therapy
  - **Timing:** Trial still ongoing; patients will be followed for up to 4 years
- **Late-breaking interim results released at ERS 2023**
  - **Efficacy:** Improvements in 6MWD, NT-proBNP, WHO FC maintained at 1 year
  - **Safety:** 93 patients (23%) had telangiectasia (none serious), including 12% who developed this in a prior phase 2 trial; 7 patients experienced 9 clinical worsening events, including 3 deaths and 3 PAH-related hospitalizations
  - **Timing:** 336 days (median duration of exposure)

FRS, French Risk Score.

Preston I, et al. ERS 2023. LBA OA739.

TORREY: Phase 2 Trial Seralutinib

- Inhaled PDGFR antagonist thought to halt vascular remodeling
- **Results from TORREY trial (NCT04456998) released at ATS 2023**
  - 86 patients with FC II or III PAH randomized to seralutinib or placebo, twice daily
  - **Efficacy:** Met primary endpoint of change in PVR at 24 weeks
    - Patients with FC II had 14.3% PVR reduction over placebo
    - Patients with FC III had 20.8% PVR reduction over placebo
  - **Safety:** mild or moderate cough

ATS, American Thoracic Society.

Frantz RP, et al. ATS 2023. Abstract D106.

Phase 2 Trial Ralinepag

- Immediate-release oral PRA being developed as add-on therapy
- **Results from a phase 2 trial (NCT02279160)**
  - 61 patients on monotherapy or dual therapy randomized to ralinepag or placebo twice daily
  - **Efficacy:** Met primary endpoint of change in PVR over 22 weeks
    - Patients on ralinepag showed 29.8% reduction in PVR over placebo
  - **Safety:** headache, nausea, and diarrhea

Torres F, et al. *Eur Respir J.* 2019;54:1901030

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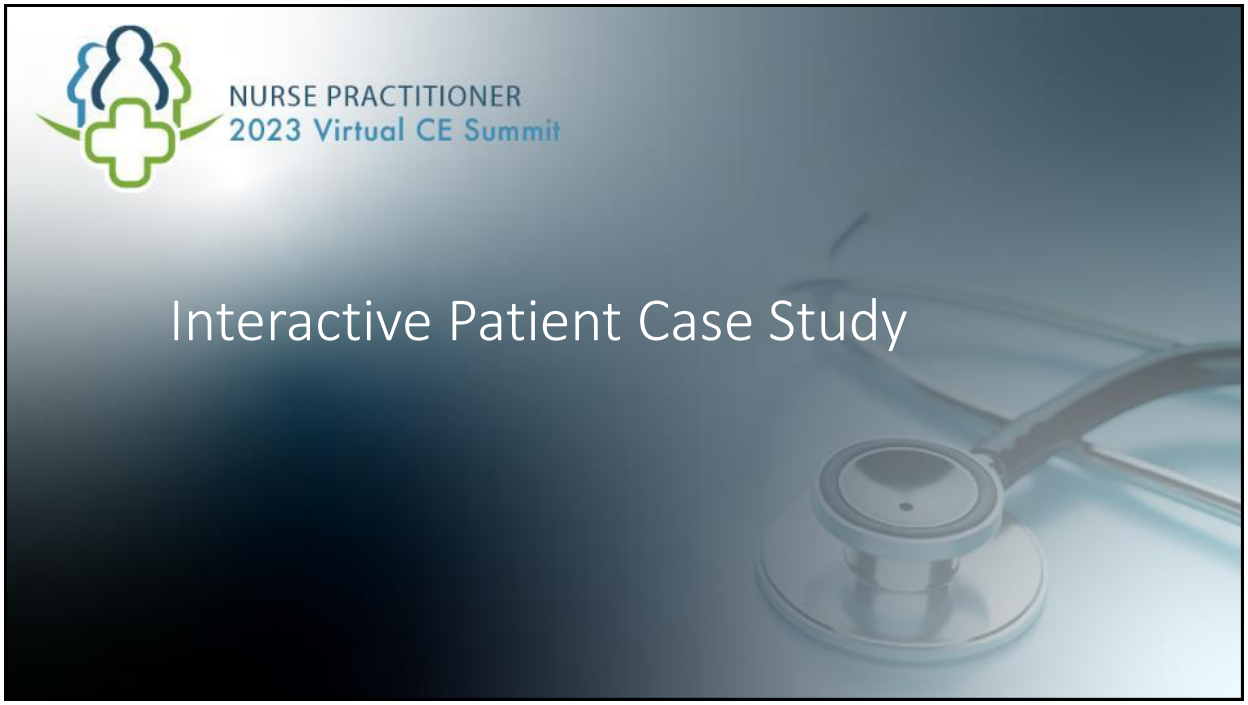


Case Study Introduction

- Adam, Caucasian, age 41, was diagnosed with PAH 9 months ago
- After 3 months of monotherapy with an ERA, he was switched to dual therapy with ambrisenten (ERA) + sildenafil (PDE-5 inhibitor)
- Now he shows worsening symptoms and is intermediate-high risk on the ERS/ESC 4-strata risk tool

? Discussion Polling Question #1

What do ERS/ESC guidelines say to do now?

A. Refer to PH center
B. Switch to a different ERA
C. Add an IV or SC PCA
D. Add an INH PCA

Responses to Polling Question #1

- This patient has entered an intermediate-high risk group
- Triple therapy is currently indicated by the ESC/ERS 2022 guidelines for an intermediate-high or high-risk patient
  - **Refer to PH center:** It's assumed this patient was already referred for accurate diagnosis and treatment
  - **Switch to different ERA:** Switching to a different drug in this class is unlikely to improve this disease process
  - **Add an IV or SC PCA:** Correct answer, per guidelines
  - **Add an INH PCA:** Not addressed by guidelines

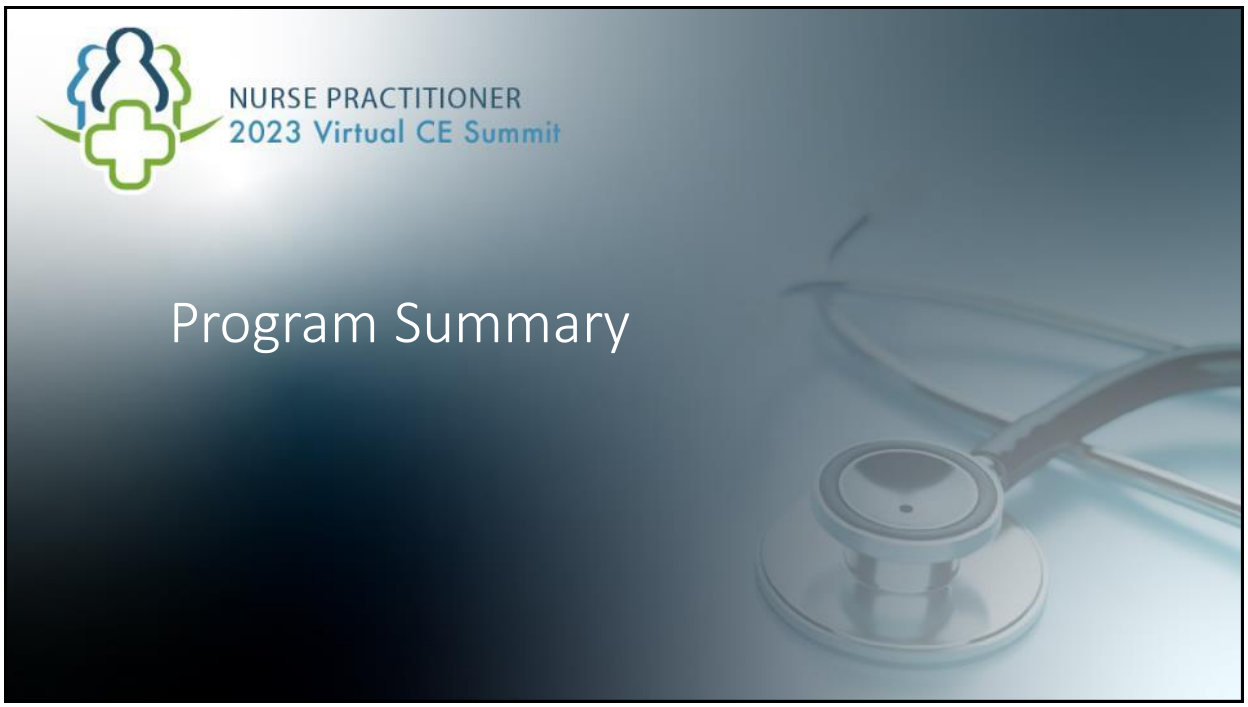
? Discussion Polling Question #2

The patient is asking about possibly adding sotatercept, a drug he heard about on social media. What is your correct response about this treatment?

A. It's not indicated for PAH
B. It works only as monotherapy
C. It's not yet FDA approved
D. It's only for Group 4 PH

Responses to Polling Question #2

- Sotatercept is currently awaiting FDA data review and potential approval
  - **It's not indicated for PAH:** Technically correct as it's not yet approved for anything, but it ***is*** being studied for a PAH indication
  - **It works only as monotherapy:** Incorrect. Sotatercept is being studied as an add-on treatment, so it would not be given as monotherapy even after approval
  - **It's not yet FDA approved:** The only correct response at this point
  - **It's only for Group 4:** Incorrect; sotatercept is being studied for PAH, which is Group I PH



Summary

- PAH is characterized by pulmonary artery remodeling eventually leading to right heart failure
- PAH is usually idiopathic and affects all ages, genders, and races but is more common in women with onset often being seen in women younger than 30 years
- NPs play an important role in early diagnostic testing, treatment monitoring, quality-of-life issues, and advocating for patients
- Multiple treatment options now available with more on the way!
- Combinations are designed to target molecular disease pathways
- Treatment guidelines recommend dual treatment for most newly diagnosed patients

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Thank You!