NURSE PRACTITIONER
2021 Virtual CE Summit

Raising the Index of Suspicion in Primary Care: Improving Referral Rates, Diagnosis, and Outcomes in Pulmonary Hypertension

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This CME activity is provided by Integrity Continuing Education. This CE activity for AANP credit is jointly provided by Global Education Group and Integrity Continuing Education.

Supporter Acknowledgement

This activity is supported by an educational grant from Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.

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Faculty Disclosures

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Consulting Fees – Actelion, Bayer, United Therapeutics

Learning Objectives

- Recognize the role for the NP to improve patient outcomes in PAH
- Differentiate symptoms and signs of PAH from disorders with similar presentations to help improve early referral and recognition of the disease
- Discuss how to develop a patient-centered, guideline-directed, evidence-based management plan for PAH that includes consideration of novel therapies and current clinical trial data
- Describe the patient experience for patients with PAH

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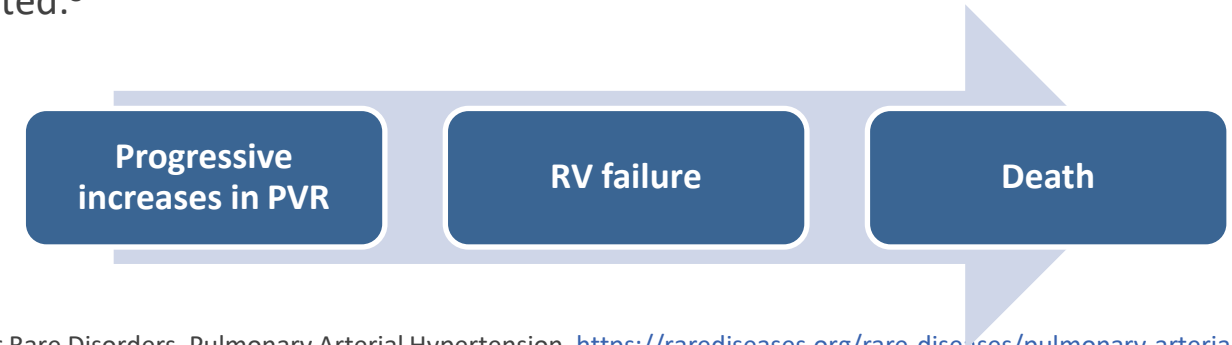
Introduction

Pulmonary Arterial Hypertension (PAH)

- Rare progressive disease[1]
- ~500–1000 new cases each year in US[1]
- More prevalent in women
- Most commonly observed in patients 60-80YO
- Most severe pulmonary hypertensive disease[2]
- If untreated:[3]



~40% of all patients die ≤5 years from diagnosis[4]

1. National Organization for Rare Disorders. Pulmonary Arterial Hypertension. https://rarediseases.org/rare-diseases/pulmonary-arterial-hypertension/
2. Vazquez ZGS, et al. *Lung*. 2020;198(4):581-596; **3**. Humbert M, et al. *N Engl J Med*. 2004;351(14):1425-1436; **4**. Farber HW, et al. *Chest*. 2015;148(4):1043-1054.

Role of the Nurse Practitioner in Diagnosing and Treating PAH

- Diagnosis, treatment, and management require a multidisciplinary team[1]
- NPs are well suited to

- Guidelines advocate early referral of patients to centers specializing in PH/PAH[1,4]

1. Klinger JR, et al. *Chest*. 2019;155(3):565-586. **2**. Doyle-Cox C, et al. *Pulm Circ*. 2019;9(2):2045894019855611. **3**. Stewart T, et al. *Pulmonary Therapy*. 2017;3:93-111. **4**. Galie N, et al. *Eur Heart J*. 2016;37(1):67–119.

When to Refer Patients to PH Center

Echocardiogram findings suspicious for PAH

High probability of PH:

- RVSP ≥35 mm Hg without left heart disease
  The is an estimate derived from the tricuspid regurgitant jet
  TR jet ≤ 2.8 is normal (approx. under 35)
- RV enlargement
- RV dysfunction

Intermediate probability: either pressure estimate is high or RV findings are present in absence of left heart disease- Refer

Low probability : normal RVSP, normal RV , findings of left heart disease: look for other causes

Galie N, et al. *Eur Heart J*. 2016;37(1):67–119.

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Diagnosis of Pulmonary Hypertension

Clinical Manifestations of Pulmonary Hypertension

Nonspecific symptoms, initially induced by exertion

- Dyspnea
- Fatigue
- Weakness
- Angina
- Syncope

Advanced cases

- Symptoms occur at rest

With progressing right ventricular failure

- Abdominal distension
- Ankle edema

Galie N, et al. *Eur Heart J*. 2016;37(1):67-119.

Differential Diagnosis

- Congestive heart failure
- Coronary artery disease
- Left heart diseases
- Valvular disease
- Cardiomyopathy
- Pulmonary embolism
- Lung diseases (eg, chronic obstructive pulmonary disease)

Galie N, et al. *Eur Heart J*. 2016;37(1):67–119; Stringham R, et al. *Am Fam Physician*. 2010;82(4):370-377; National Organization for Rare Disorders. Pulmonary Arterial Hypertension. https://rarediseases.org/rare-diseases/pulmonary-arterial-hypertension/

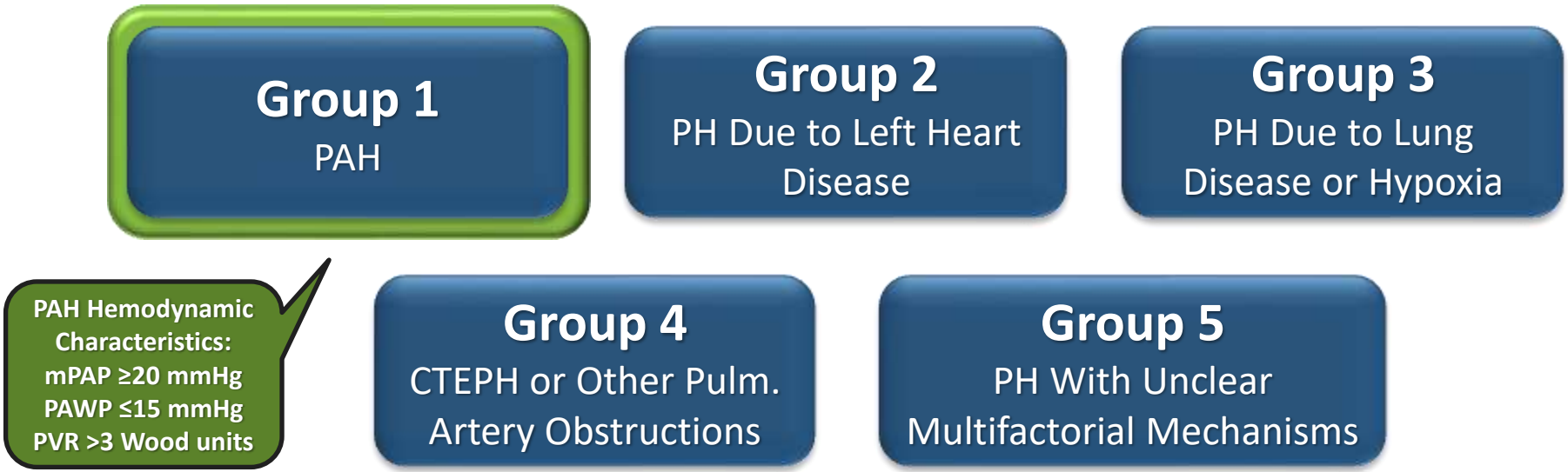
Components of Diagnostic Evaluation

- Early referral and recognition
- Echocardiography
- Ventilation/perfusion scan
- Pulmonary Function Tests
- Chest CT (usually HRCT)
- Biomarkers (BNP or NT-proBNP)
- 6-minute walk test
- Right heart cath/hemodynamic diagnosis

BNP, brain natriuretic peptide; CT, computed tomography; NT-proBNP, N-terminal pro-BNP.

Galie N, et al. *Eur Heart J*. 2016;37(1):67–119; Klinger JR, et al. *Chest*. 2019;155(3):565-586; Frost A, et al. *Eur Respir J*. 2019;53(1):1801904.

WHO Classification of Pulmonary Hypertension



CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery preassue; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

Galie N, et al. *Eur Respir J.* 2019; 53 1801889.

Subcategories of Group 1: PAH

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 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
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

PVOD, pulmonary veno-occlusive disease.

Galie N, et al. *Eur Respir J.* 2019; 53 1801889.

Updated Classification of Drugs/Toxins Associated with PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St. John's wort
Methamphetamines	Amphetamine
Dasatinib	Interferon-α and -β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

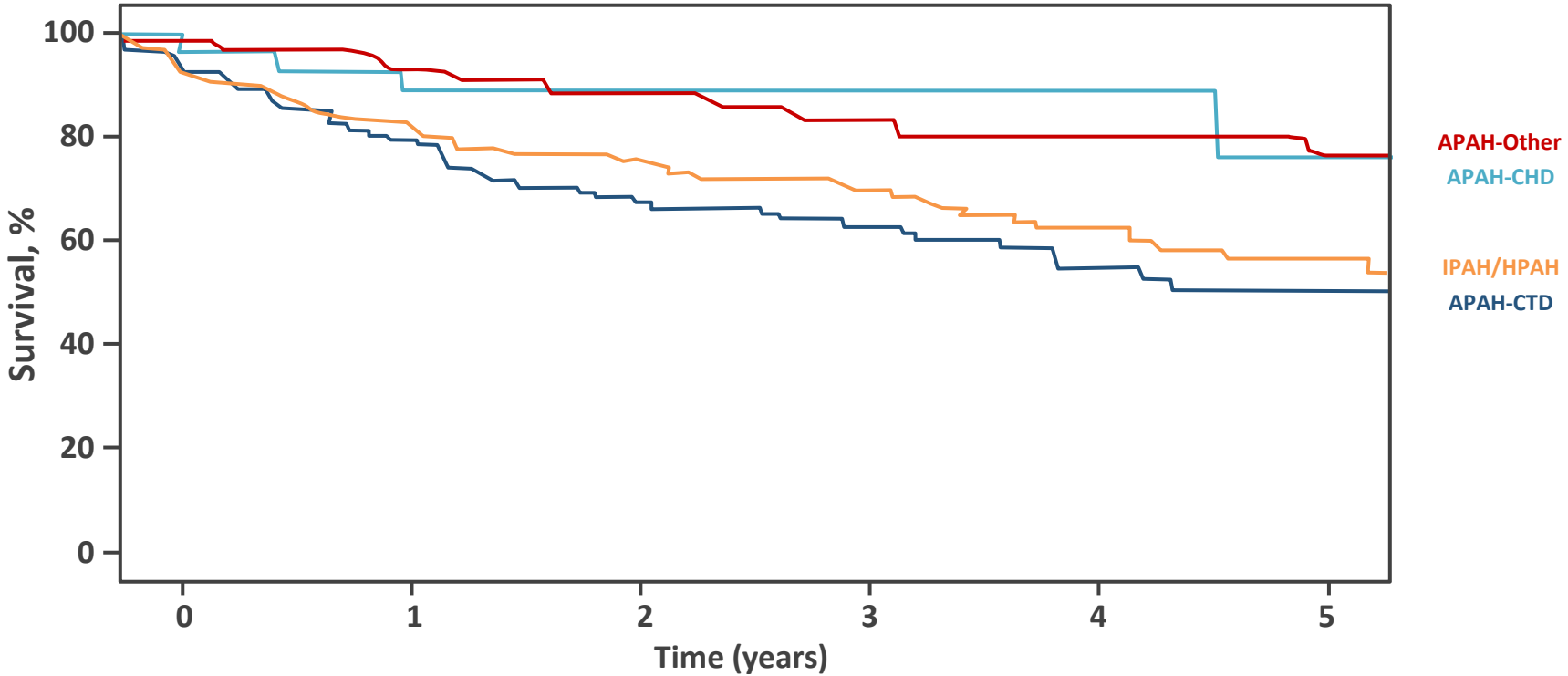
Simonneau G, et al. *Eur Respir J.* 2019;53:1801913.

WHO Functional Classification of PH*

WHO-FC	Description
I	• No limitation of physical activity • Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	• Slight limitation of physical activity • Comfortable at rest • Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	• Marked limitation of physical activity • Comfortable at rest • Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	• Unable to carry out any physical activity without symptoms • Manifest signs of right heart failure • Dyspnea and/or fatigue may even be present at rest • Discomfort increased by any physical activity

*Functional classification of pulmonary hypertension modified after the New York Heart Association functional classification according to the WHO 1998. Galiè N, et al. *Eur Heart J*. 2009;30(20):2493-537.

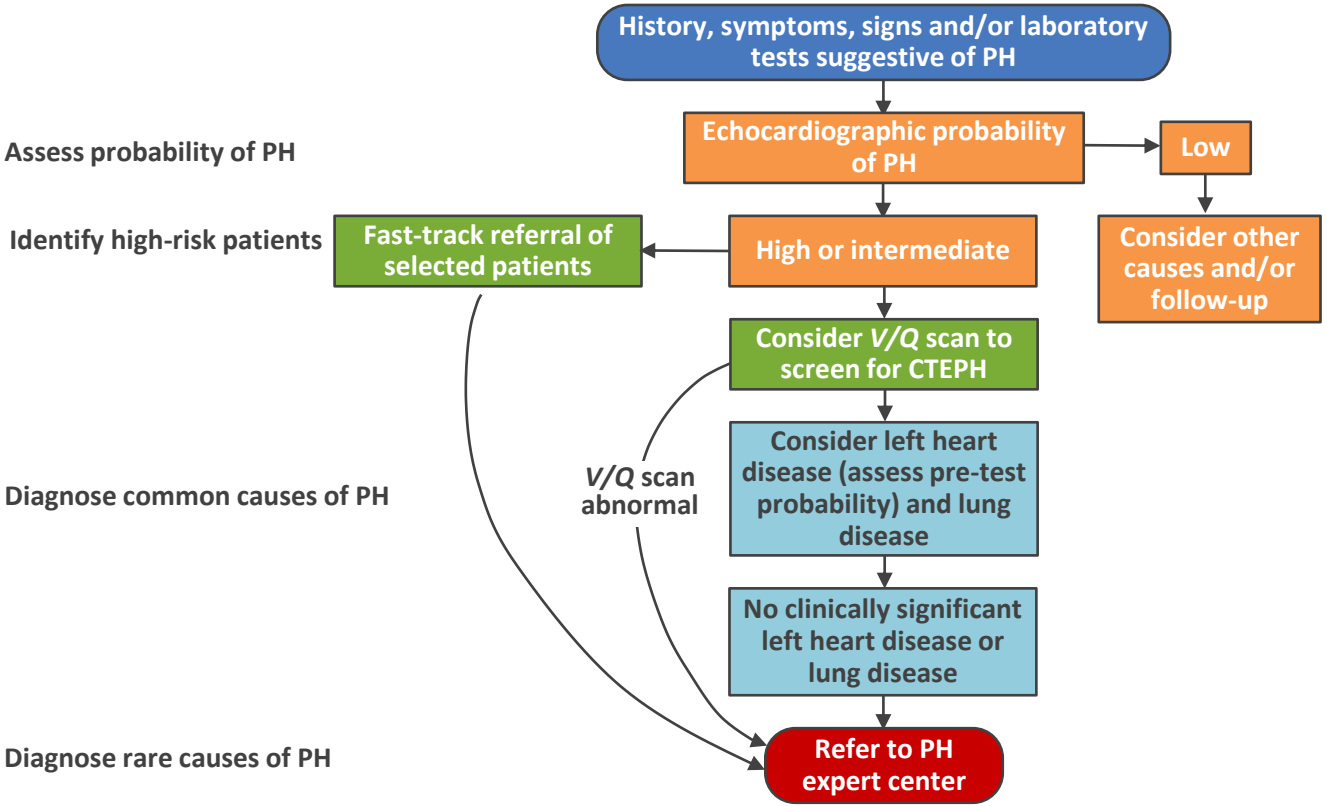
Importance of Early Recognition in PAH



APAH, associated PAH; CHD, congenital heart disease; CI, confidence interval; CTD, connective tissue disease; HPAH, hereditary PAH; HR, hazard ratio; IPAH, idiopathic PAH; SSc, systemic sclerosis.

Rådegran G, et al. *Scand Cardiovasc J*. 2016;50(4):243-250; Humbert M, et al. *Arthritis Rheum*. 2011;63(11):3522-30.

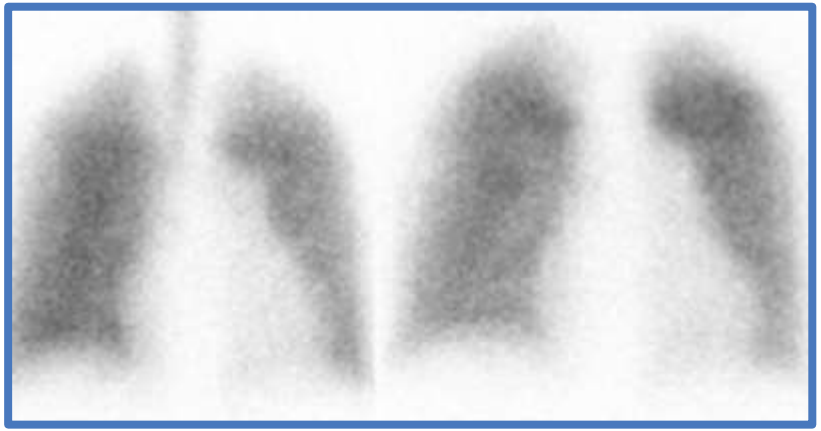
Diagnostic Algorithm: 2018 6th World Symposium



Adapted from Frost A, et al. *Eur Respir J.* 2019; 53 1801904.

V/Q Scan

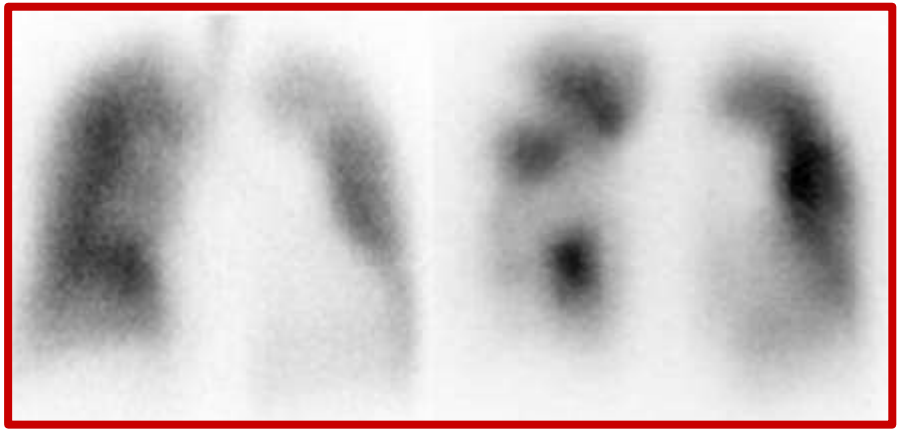
Ventilation **Perfusion**



Normal or Mottled Pattern

PAH

Ventilation **Perfusion**

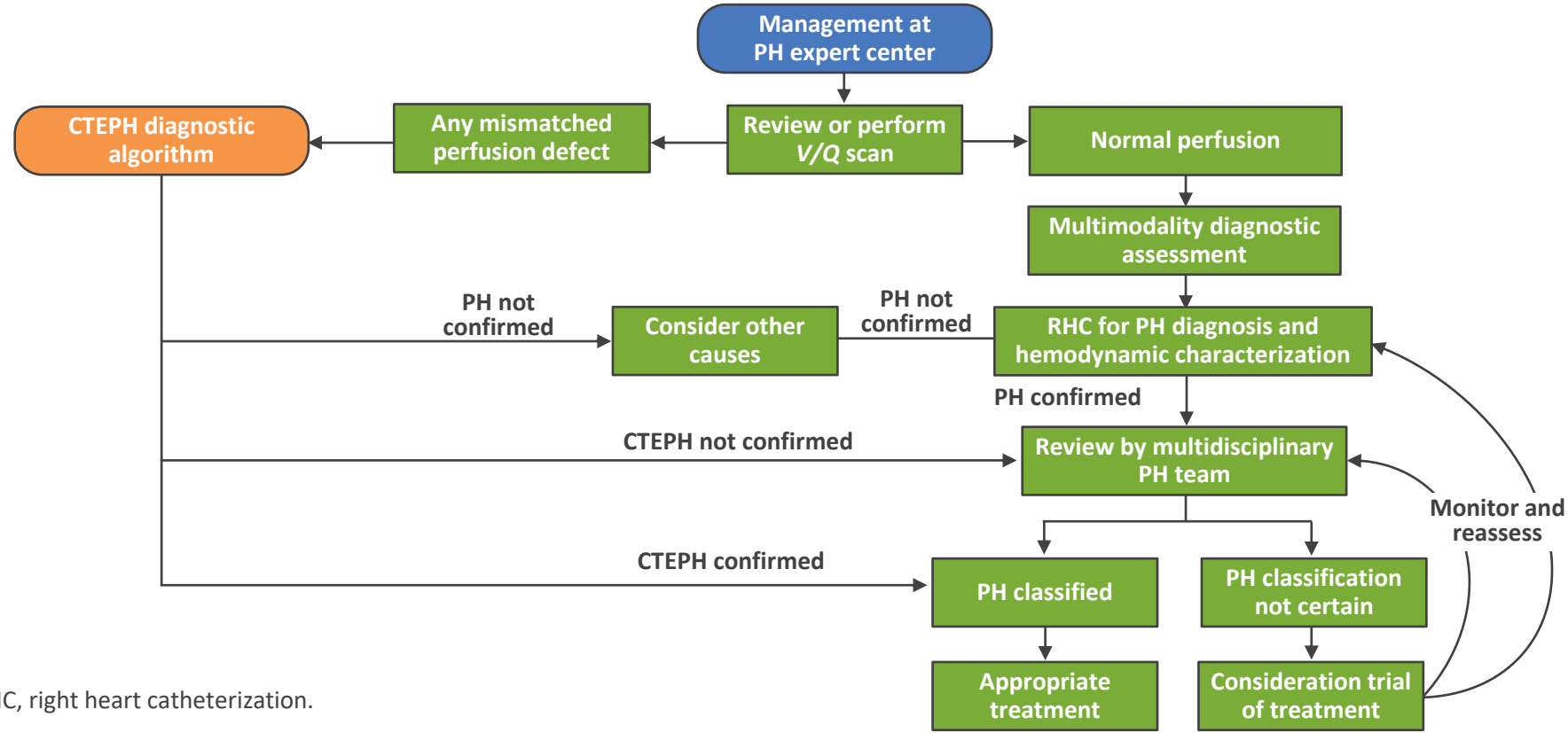


At least one segmental perfusion defect inconsistent with ventilation scan findings

CTEPH

Tanabe N, et al. *Respir Investig*. 2013;51(3):134-146.

Diagnostic Algorithm: 2018 6th World Symposium



RHC, right heart catheterization.

Adapted from Galie N, et al. *Eur Respir J*. 2019; 53 1801889.

Risk Assessment of PAH

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%

*Mostly based on expert opinion and validated for IPAH. RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; VCO_2, carbon dioxide output; VO_2, oxygen uptake. Galie N, et al. *Eur Heart J*. 2016;37(1):67–119.

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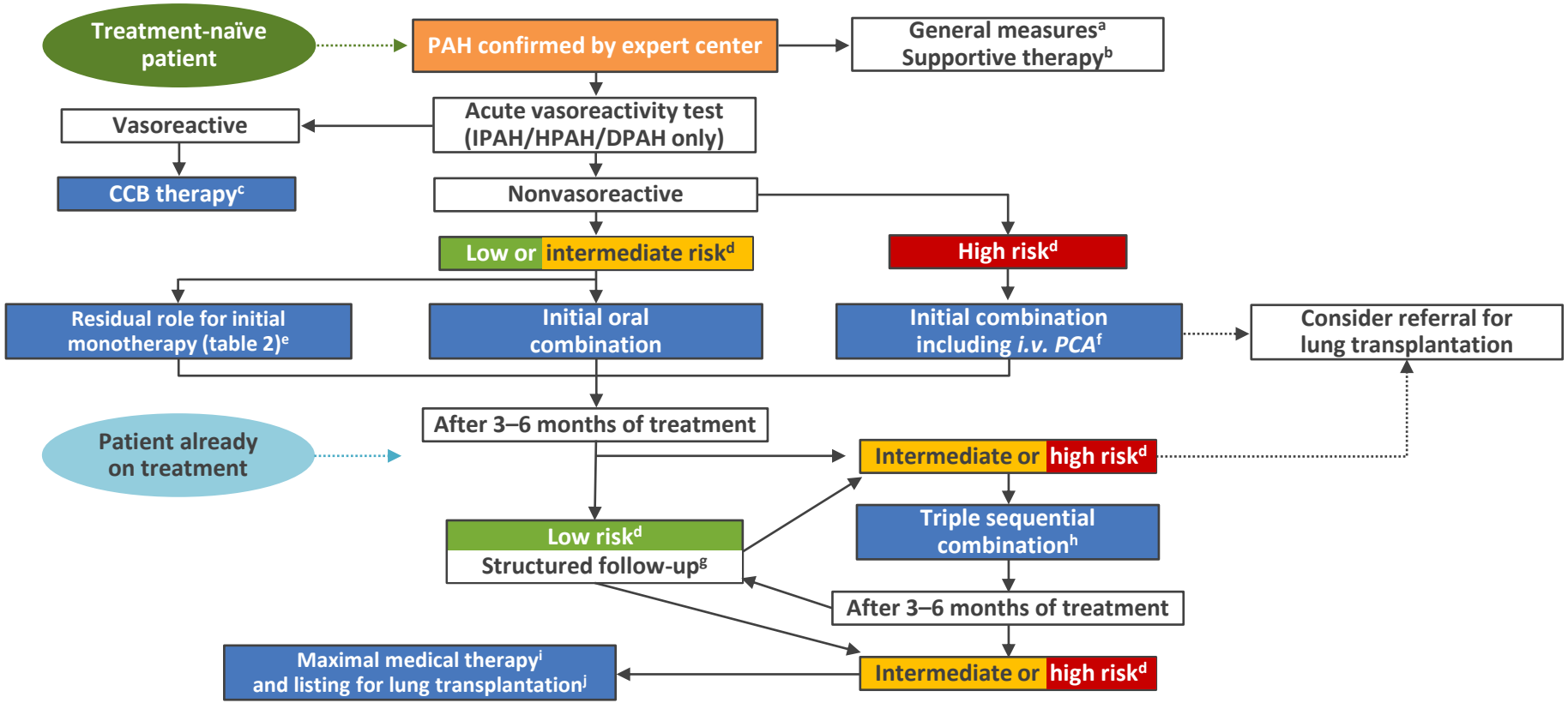
Pharmacologic Therapy and Guidelines for Management

2018 6th World Symposium Recommendations



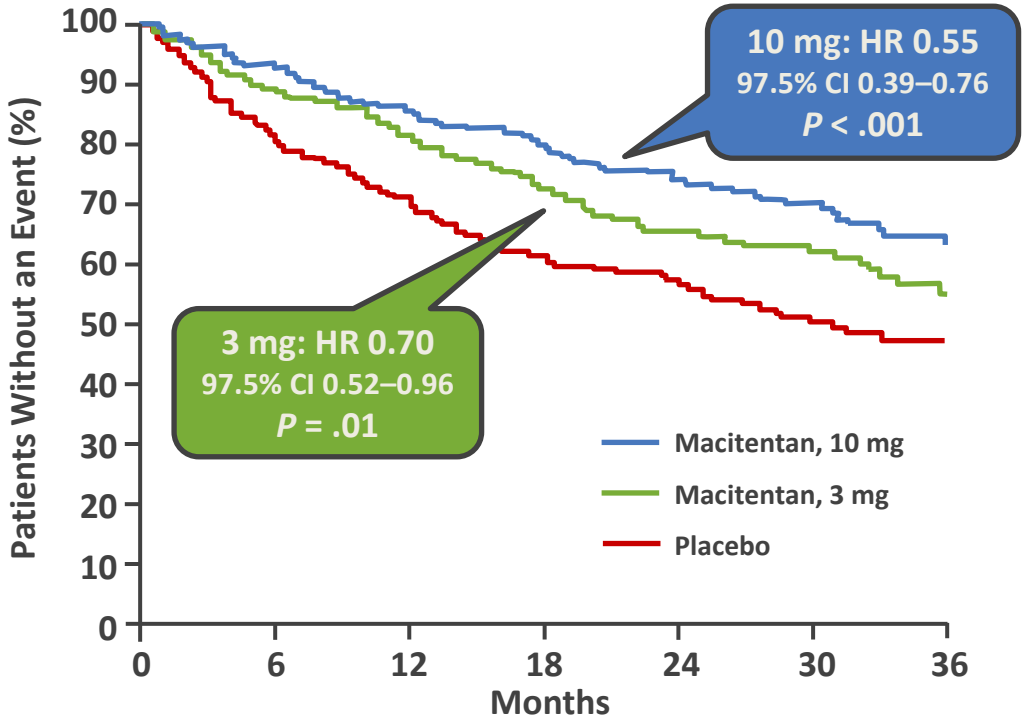
Adapted from Galie N, et al. *Eur Respir J*. 2019; 53 1801889.

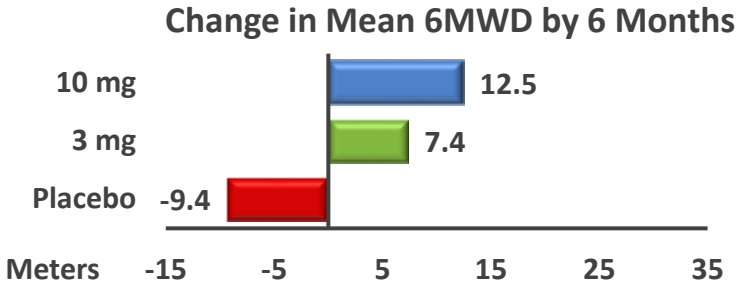
Monotherapy Is Now the Exception

- FC I or II patients
- Long term success with monotherapy
- Older patients with evidence of Group 2 component
- Patients suspected of having PVOD
- POPH or HIV patients as they were not included in RTC
- Very mild PH with normal right heart findings
- Combination therapy is contraindicated

Galie N, et al. *Eur Respir J.* 2019; 53 1801889.

Macitentan: SERAPHIN Trial



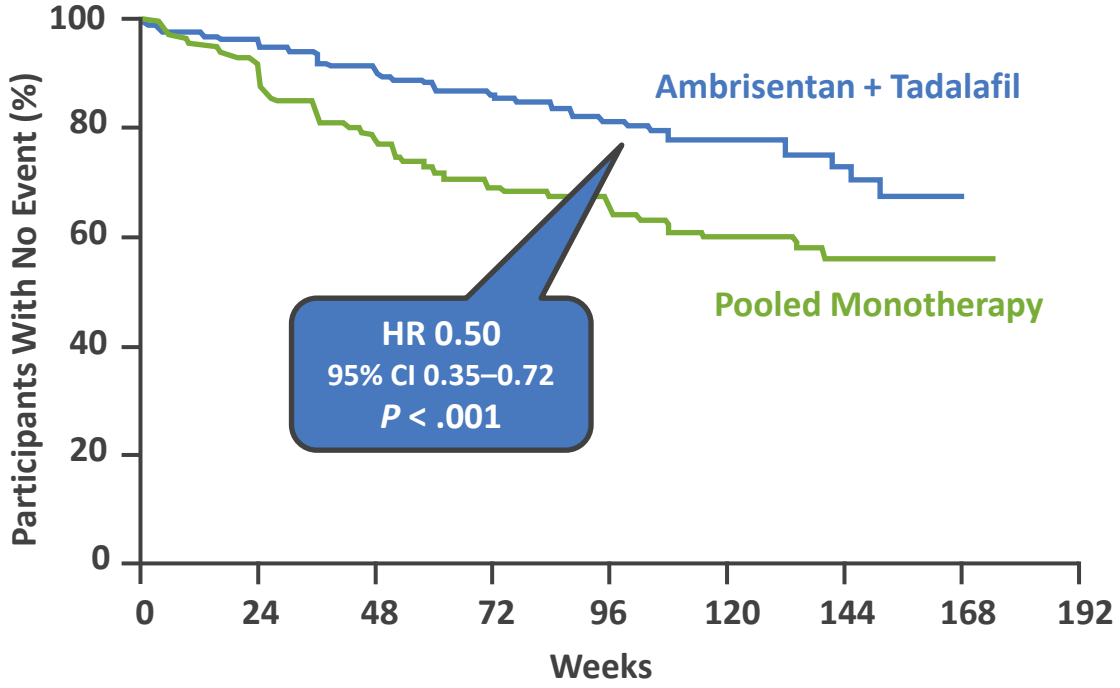


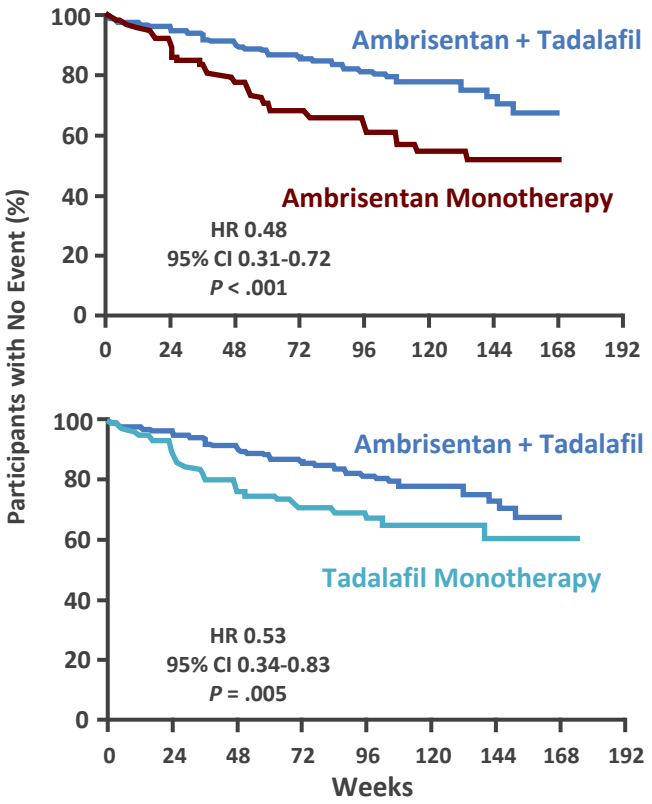
Common Adverse Events	10 mg (n = 242)	3 mg (n = 250)	Placebo (n = 249)
Worsening PAH	22%	30%	35%
Upper respiratory tract infection	15%	20%	13%
Peripheral edema	18%	16%	18%
Nasopharyngitis	14%	15%	10%
RV failure	13%	15%	22%
Headache	14%	13%	9%

6MWD, 6-minute walking distance.

Adapted from Pulido T, et al. *N Engl J Med*. 2013;369(9):809-818.

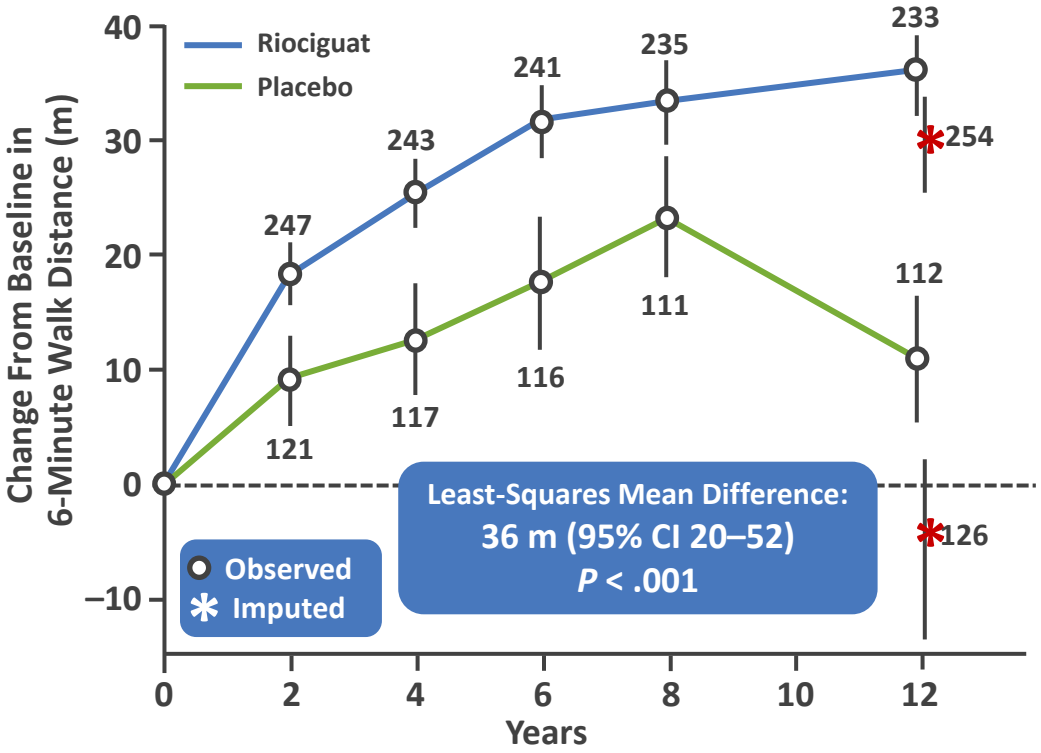
The AMBITION Trial: Evidence for Combination Therapy

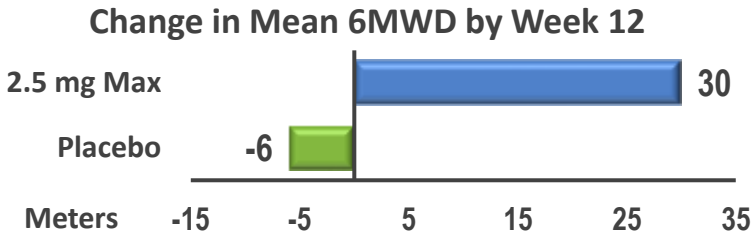




Adapted from Galiè N, et al. *N Engl J Med*. 2015;373(9):834-844.

Riociguat: PATENT Trials

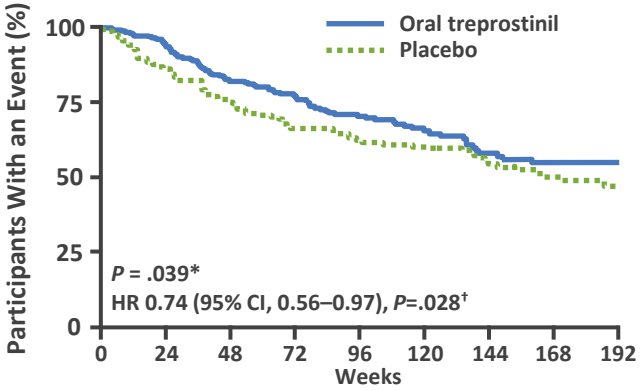


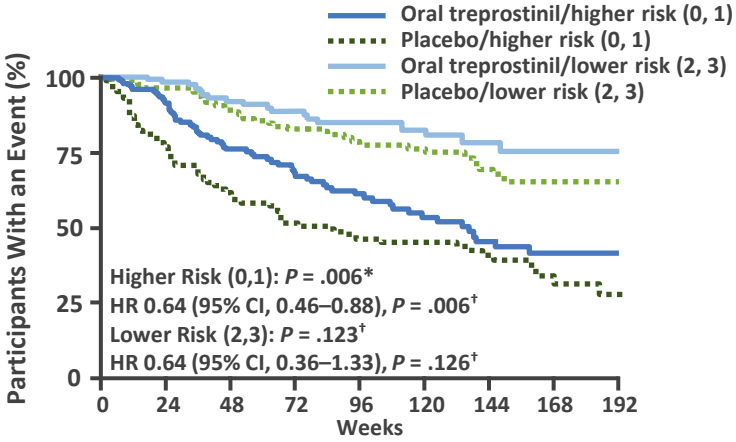


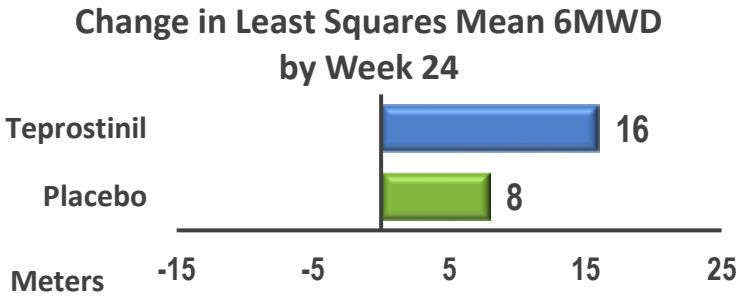
Common Adverse Events	2.5 mg max (n = 254)	1.5 mg max (n = 63)	Placebo (n = 126)
Headache	27%	32%	20%
Dyspepsia	19%	13%	8%
Peripheral edema	17%	22%	11%
Nausea	16%	16%	13%
Dizziness	16%	24%	12%
Diarrhea	14%	10%	10%

Ghofrani H-A, et al. *N Engl J Med*. 2013;369(4):330-340.

Teprostinil: FREEDOM-EV Trial



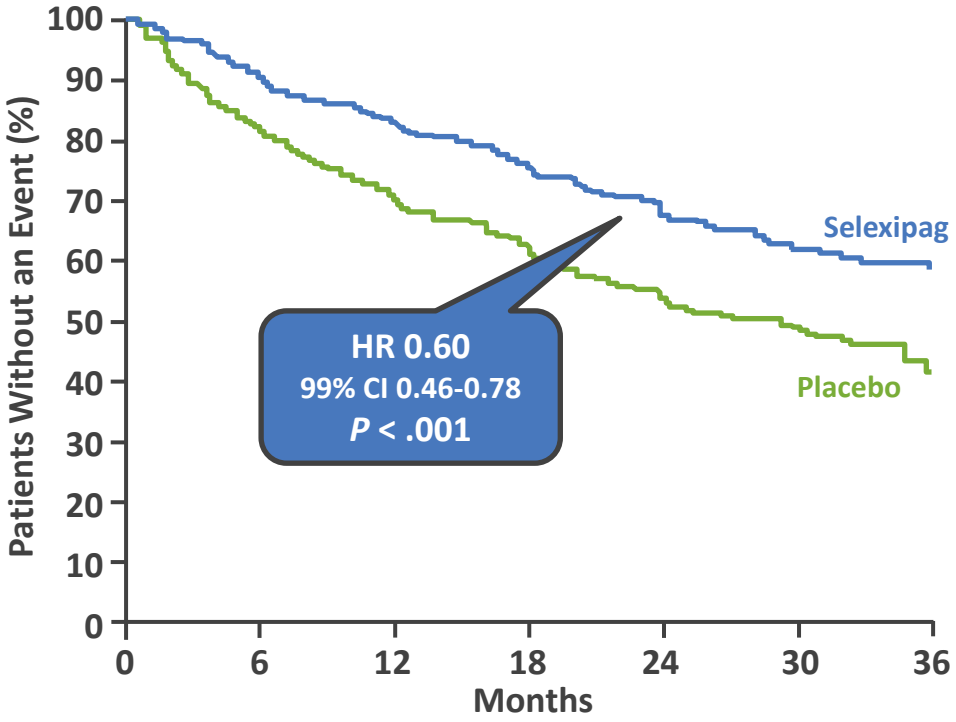


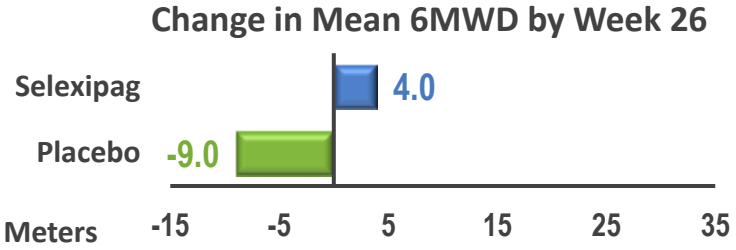


Common Adverse Events	Teprostinil (n = 346)	Placebo (n = 344)
Headache	70%	30%
Diarrhea	66%	20%
Flushing	44%	8%
Nausea	37%	17%
Vomiting	32%	8%
Pain in jaw	17%	2%

White RJ, et al. *Am J Respir Crit Care Med*. 2020;201(6):707-717.

Selexipag Mono-, Double, or Triple Therapy GRIPHON Trial





Common Adverse Events	Selexipag (n = 575)	Placebo (n = 577)	*P* value
Headache	65%	33%	<0.001
Diarrhea	42%	19%	<0.001
Nausea	34%	19%	<0.001
Pain in jaw	26%	6%	<0.001
Worsening of PAH	22%	36%	<0.001
Vomiting	18%	9%	<0.001

Adapted from Sitbon O, et al. *N Engl J Med*. 2015;373(26):2522-2533.

The TRITON Trial: Evidence for Combination Therapy

Initial triple PO therapy (selexipag + macitentan, + tadalafil) vs initial double oral therapy (macitentan + tadalafil)

Variable	Initial Triple Therapy	Initial Double Therapy	Ratio (95% CI) *P* value
	Reduction (%)	Reduction (%)	
PVR (Wood units)	54	52	0.96 (0.86–1.07) *P* = .424
NT-proBNP (ng/L)	74	75	1.03 (0.77–1.37) *P* = .853
	Least-squares mean (95% CI) change from baseline to week 26	Least-squares mean (95% CI) change from baseline to week 26	Difference (95% CI) *P* value
6MWD (m)	+55.0 (40.4–69.5)	+56.4 (41.4–71.3)	−1.4 (−19.4 to 16.5) *P* = .876

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

HR 0.59
(95% CI 0.32-1.09)
***P* = .087**

Data are mean (SD) unless otherwise stated.
PO, by mouth.
Chin K, et al. *Am J Respir Crit Care Med*. 2020;201:A2928.

No difference between treatment regimens at week 26

Transitioning From IV to Oral Therapy

- Switching from IV to oral prostacyclins in patients with clinically stabilized PAH may reduce risks of long-term IV therapy
- Recent study: 14 patients attempted a switch from IV prostacyclins to PO selexipag using a standardized protocol
  - 2 patients required an additional oral therapy
  - Assessments showed stable hemodynamics, NT-proBNP, and functional capacity
  - RV function remained stable in all but 1 patient
    - Worsened from normal to mild RV dysfunction, but was otherwise stable
  - After median of 23.7 months
    - All but 1 patient was alive and remained on selexipag
    - None required parenteral therapy
    - 1 patient died due to worsening liver failure

Parikh KS, et al. *J Cardiovasc Pharmacol*. 2020;75(4):299-304.

Dose Titration

- Optimal dosing of PAH therapies varies widely
- Dose titration is required to balance treatment effectiveness and adverse reactions while maximizing patient adherence
- Essential to implement up-to-date practices:
  - Specific titration methods
  - Frequent monitoring
  - Open communication with patients

Lombardi S, et al. *Respir Med*. 2018;143:139-146.

Prostacyclin Adverse Event Management

- Most patients experience significant side effects with prostacyclin therapy
- Proactive side effect management will help increase patient adherence
- Patients should be educated to expect side effects

Therapy	Route	Common Side Effects	
		Related to Route	Related to MOA
Epoprostenol	IV	Catheter-related infections, sepsis, thromboembolic event, bleeding, drug-delivery system malfunction	Jaw pain, diarrhea, flushing, headaches, nausea, vomiting
Iloprost	INH	Cough, throat irritation	Flushing, jaw pain, headaches, hypotension, body aches, nausea, diarrhea, dizziness
Treprostinil	PO	Pill shell may not be absorbed and may be visibly excreted in the feces	Headaches, flushing, nausea, diarrhea, jaw pain, vomiting, extremity pain
	SC	Infusion site pain, site reaction, and site abscess	Diarrhea, jaw pain, flushing, nausea, rash, dizziness, vomiting, headaches, flushing
	IV	Catheter-related infections, thromboembolic event, drug-delivery system malfunction	Extremity pain, headaches, diarrhea, jaw pain, nausea, fatigue, loose stools, vomiting, dizziness, dyspnea, flushing, palpitations, peripheral edema
	INH	Cough, throat irritation, pharyngolaryngeal pain	Headaches, nausea, flushing, diarrhea, dizziness
Selexipag	PO	N/A	Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing

INH, inhaled; MOA, mechanism of action; SC, subcutaneous.

Kingman M, et al. *Pulm Circ*. 2017;7(3):598-608.

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Patient-Directed Therapy

The Patient Perspective

- Consider patient goals and preferences
  - Eg, improve quality of life, reduce burden of complex therapies
- Improve communication
  - Encourage patients to express their perspectives
  - Be receptive and incorporate their views into management
- Provide opportunities for support
  - Encourage participation in patient advocacy groups that allow patients and caregivers to share their experience and collaborate with others
  - Pulmonary Hypertension Association: https://phassociation.org/
  - Navigating PAH Pathways: www.navigatingpah.com
  - myPHteam: https://www.myphteam.com/
- Health-related quality of life (HRQoL)
  - PAH negatively impacts HRQoL and therapies can have variable effects
  - Some measures of HRQoL correlate with survival
  - Can improve HRQoL by addressing concomitant health issues

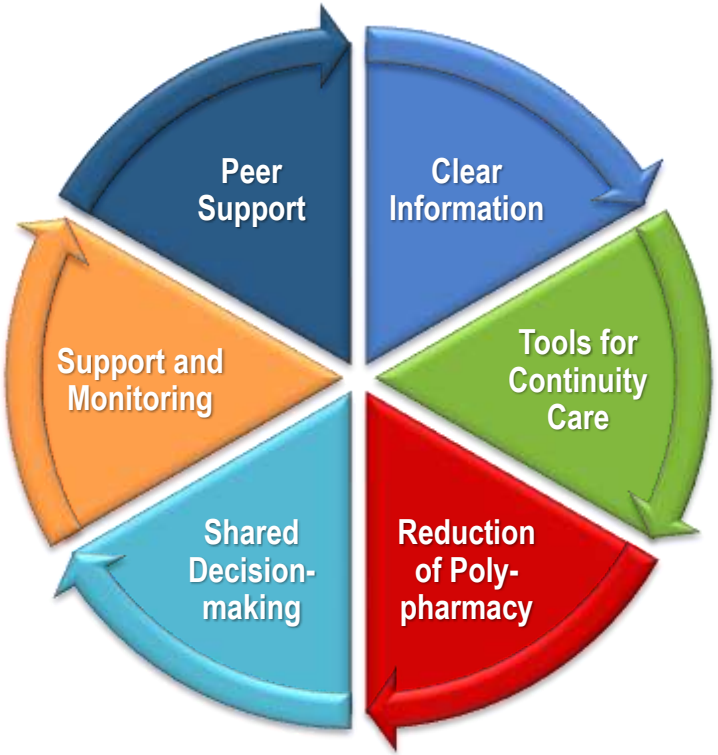
PHA Pulmonary Hypertension Association
Empowered by hope

NAVIGATING PAHPATHWAYS
Knowledge. Understanding. Empowerment.

myPHteam

McGoon MD, et al. *Eur Respir J*. 2019;53(1):1801919.

Addressing Adherence Issues

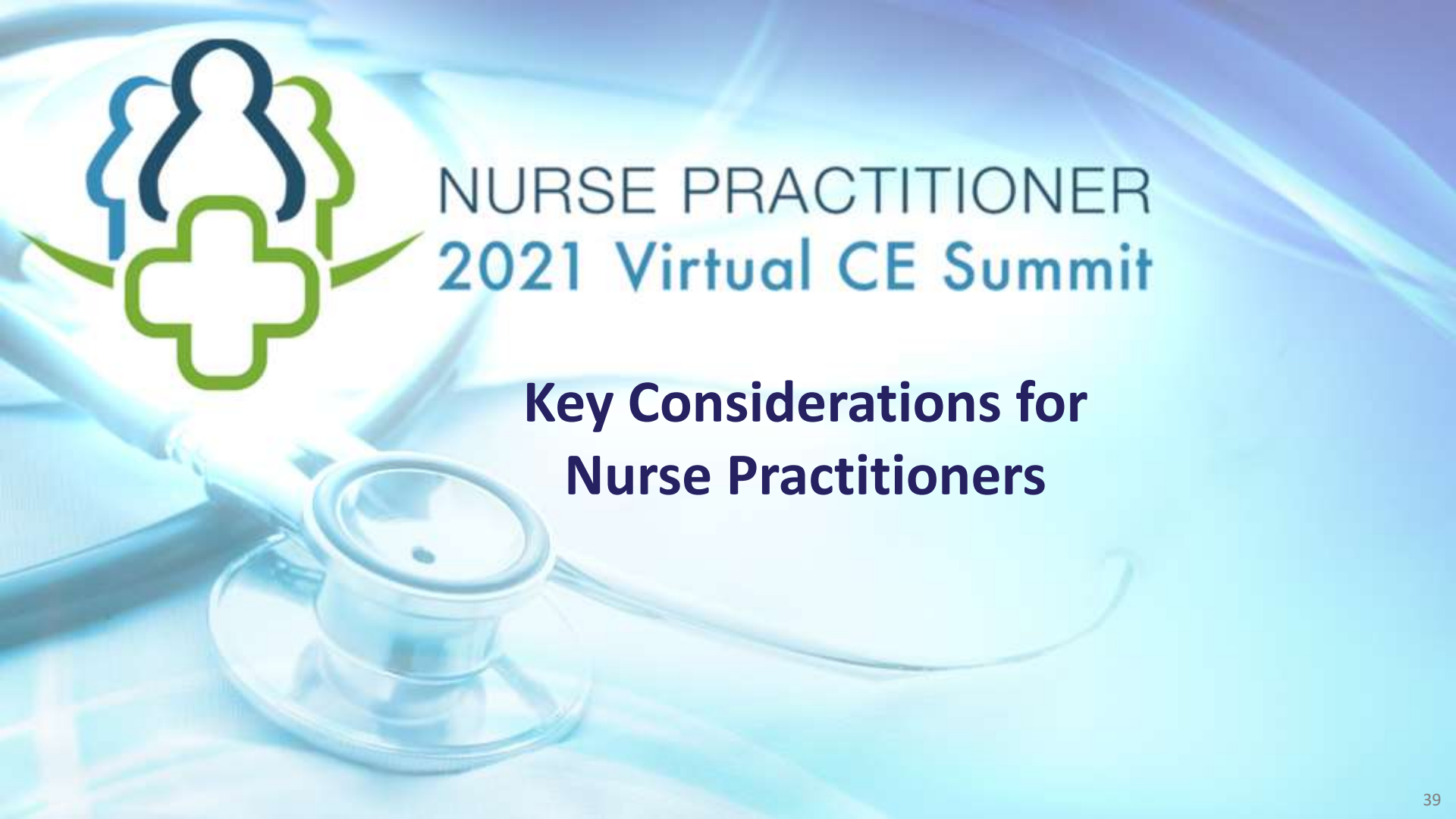


- Shared decision making
- Tools to assist with adherence
- Awareness of limitations in older patients
- Help with low health literacy
  - Simple language
  - Larger font sizes
  - Pictures/diagrams

Nurse-specific Training

- IV prostacyclin therapy
  - Medication orders
  - IV access
  - Initiation of therapy
  - Safety measures
  - Catheter priming for concentration changes or line changes
  - Pump management and maintenance
  - Care of central line and patient education
- Transitioning from one IV prostacyclin to another

Kingman MS, Lombardi S. *J Infus Nurs*. 2014;37(6):442-451.



Key Considerations for Nurse Practitioners

Key Considerations for Nurse Practitioners

- Ensure adequate patient and caregiver support
  - Serve as support resource for patients, families, and staff
  - Provide follow-up care in clinic for PAH patients
  - Guide patients and families through treatment decisions
- More than half of patients receive inappropriately prescribed therapy
  - Be familiar with patient-centered, guideline-directed, evidence-based management
  - Monitor treatment response and adjust therapies
  - Refer for palliative care where appropriate

Doyle-Cox C, et al. *Pulm Circ*. 2019;9(2):2045894019855611; Stewart T, et al. *Pulmonary Therapy*. 2017;3:93-111; Deaño RC, et al. *JAMA Intern Med*. 2013;173(10):887-93.

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Case Study Polling Questions

Case Study Polling Question 1

A 46-year-old woman presents with dyspnea, weakness, chest pain, a dry cough, and swelling in her ankles. You suspect that the patient may have PH.

1. **What is the first step you should take in diagnosing this patient?**
   A. Perform a V/Q scan
   B. Determine the patient's echocardiographic probability of PH
   C. Rule out other diagnoses that may be causing these symptoms
   D. Refer the patient to a PH center for specialized care

Case Study Polling Question 2

A 46-year-old woman presents with dyspnea, weakness, chest pain, a dry cough, and swelling in her ankles.

You confirm a diagnosis of PAH by right heart catheterization. The patient reports that ordinary physical activity aggravates her symptoms.

2. How will you treat this patient?

A. The patient falls under WHO-FC I and should be monitored for progression

B. The patient falls under WHO-FC II and should be prescribed monotherapy or combination therapy for PAH as tolerated

C. The patient falls under WHO-FC III and should be prescribed monotherapy or combination therapy for PAH as tolerated

Case Study Polling Question 3

A 46-year-old woman presents with dyspnea, weakness, angina, a dry cough, and swelling in her lower legs and syncope.

You confirm a diagnosis of PAH FC III with RV dysfunction. The patient reports that ordinary physical activity aggravates her symptoms.

3. The patient does not prefer IV therapy. How will you advise her?

A. The patient's preferences should be taken into consideration and oral therapies should be prescribed instead

B. You should advise the patient that IV therapies are recommended for her PAH and reassure her that it will not be overly burdensome

Case Study Polling Question 4

A 46-year-old woman presents with dyspnea, weakness, angina, a dry cough, and leg swelling.

After 3 months on combination oral therapy her symptoms and test results have not changed.

4. How will you manage this patient

A. Evaluate whether the patient is eligible for lung transplant

B. Reassess the patient's condition and prescribe 2 additional classes of therapies to her regimen

C. Reassess the patient's condition and add another class of therapy to her regimen

D. Add a prostacyclin therapy and consider referral for lung transplantation

Program Summary

- PAH is a rare progressive disease associated with significant morbidity and mortality
- NPs are best positioned to
  - Recognize and refer patients for specialized care
  - Assist with side effect management, medication titration, and adherence
  - Educate patients
- Familiarity with treatment algorithms is important to ensure appropriate disease management
- Involve patients in decision making to ensure that their goals are being met


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Thank You!